

## **CANCER STUDIES**

# **Cancer of the Breast**

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CANCER OF THE BREAST is the most common and in numbers the most lethal malignant lesion in females. It is estimated that there will be 64,000 new cases and 25,000 deaths from it in 1963, in the United States.

As a result of its high incidence and the accessibility of the breast and adjacent structures to examination and therapeutic attack it has been subjected to more thorough clinical study than any other cancer. Much of our knowledge concerning the behavior and life history of cancer in general has been derived from study of this disease.

The therapy of cancer of the breast is currently one of the most controversial areas in the treatment of malignant disease. The literature contains conflicting reports relative to the best methods of therapy, based principally upon statistical studies and their interpretation.

Certain paradoxes exist. In general the five-year survival rates have been improving but the mortality rate has remained substantially constant over the past four decades.<sup>31</sup> It is difficult to reconcile these facts.

The almost progressive improvement of results in individual institutions has been criticized as representing "selected series." The extensive material accumulated by the California Tumor Registry and the Connecticut Cancer Registry negates this criticism.

Some observers have claimed that our therapeutic efforts have produced no change in the inexorable course of this disease. It has been postulated that the improvement in five-year survival results solely from earlier recognition and, therefore, a longer period of observation of the disease. Broad generalizations of this nature have serious defects but are thought-provoking.

We cannot be complacent about the present results of therapy. Current methods have been challenged and approaches hopefully designed to improve results have been introduced or reintroduced.

There are different schools of surgical therapy. One of them has extended the standard Halsted-Willy Meyer operation to include the internal mammary chain of nodes and others have gone further

to include the supraclavicular and even the mediastinal nodes. This is an effort to encompass the disease surgically. Another group proceeds on the assumption that simple mastectomy will cure patients whose disease is limited to the breast and that if any metastasis has taken place no cure can be effected.

Neither approach is new. Simple mastectomy was employed long before the development of the conventional radical operation and largely discarded in favor of the latter. Extended radical procedures were tried by Halsted and abandoned because of the attendant morbidity and mortality and the failure to improve results.

Haagensen has addressed himself to an effort to eliminate futile and perhaps harmful application of the usual radical operation by triple biopsy.<sup>14</sup> The diagnosis is established by biopsy of the tumor. The extent of the disease beyond the breast is estimated by biopsy of the apical axillary nodes and of the internal mammary nodes of the upper three interspaces. If nodal metastasis is found the disease is considered inoperable and the patient receives therapeutic irradiation. If widely applied, these criteria of operability unquestionably would improve the results of the standard radical operation—but would they improve the overall results of therapy? There is some evidence that internal mammary node biopsy may not be a harmless procedure.<sup>19</sup>

The concept of "biologic predeterminism" advanced by Macdonald has been misunderstood and subjected to unjustified criticism.<sup>26</sup> The substance of it is that, as a result of little understood biologic factors inherent in the tumor cells or in the mechanism of host resistance or both, cancer of the breast falls into three categories. In one, the tumor is indolent and almost any form of therapy which will remove it will suffice. In another, the tumor has such aggressive characteristics that no form of therapy will be curative. In the group between these extremes, prompt and adequate treatment is important. Every surgeon experienced in the treatment of carcinoma of the breast recognizes the existence of these groups. The difficulty in application of this knowledge lies in the fact that there is no reliable method of determining into which cate-

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gory a clinically operable cancer of the breast may fall.

McWhirter, because of his dissatisfaction with the results of radical mastectomy in Edinburgh, undertook to treat patients by simple mastectomy and heavy irradiation.<sup>28</sup> His method has a few supporters in the United States.<sup>11</sup> His statistics are based upon unselected cases but are subject to serious criticism as pointed out by Ackerman and others.<sup>1,3</sup>

Irradiation, as a sole therapeutic agent or as an adjunct to surgical operation, has enjoyed varying popularity over the years. It is seldom curative when employed alone. Preoperative irradiation has been largely discarded. Postoperative irradiation is extensively employed, particularly in cases with axillary metastasis. There is a conviction on the part of some surgeons that it has value but this is difficult to establish on a statistical basis. Some observers believe it has no value. Others advise withholding irradiation until recurrence has taken place, and the effect is apparently the same.<sup>32</sup> There is some evidence suggesting postoperative irradiation may be harmful rather than beneficial.<sup>8</sup>

Ablative and additive hormone therapy have come into greater prominence, particularly in disseminated and recurrent disease. What part they may play in the attack upon clinically curable cancer of the breast remains to be determined.

Chemotherapy used in conjunction with surgical operation is under intensive study. The agents employed leave much to be desired. While the early results are suggestive of some benefit, time will be required for final evaluation.

It is obvious that our treatment of cancer of the breast, although statistically improving and requiring no apology, cannot be considered truly satisfactory. If it were, there would be general agreement concerning it, and the multiple approaches in the effort to solve the problem would not exist.

In the broad effort to improve our therapy the challenging of accepted concepts has the value of stimulating new attitudes and new procedures. Some of these may add to our knowledge and our capacity to deal with the disease.

At this stage one cannot be dogmatic. Too many questions remain to be answered. On the other hand one should not desert procedures of established value or follow proposed new methods of inadequately proven worth, except for purposes of investigation under controlled conditions in appropriate institutions.

It will be our effort to outline a plan of dealing with cancer of the breast based upon the most widely accepted principles of cancer diagnosis and therapy. This is the wise course to follow during this period of confusion and controversy.

## EARLY CANCER

Truly early carcinoma of the breast is seldom found except as the result of microscopic examination incidental to the removal of breast tissue for another condition. Cancer begins from microscopic foci which require variable and unknown periods of time to become clinically apparent.

Early clinical recognition is dependent upon the palpation of a small lump within the breast. The nature of a small lump cannot be determined by physical examination and must be established by microscopic examination of representative tissue.

When signs clinically confirming the diagnosis are present—such as skin or nipple fixation or retraction—one is no longer dealing with clinically early disease. Skin retraction over a palpable mass can be produced by traumatic fat necrosis and may lead to an erroneous clinical diagnosis of cancer.

Clinically early carcinoma of the breast rarely produces symptoms. Occasionally a mild stinging or burning sensation may attract a woman's attention to some part of the breast and result in the discovery of a lump. About 90 per cent of lumps are found by accident.

Public education efforts have induced an increasing number of women to examine their breasts at the same time in every menstrual cycle or the same date in every month if they are postmenopausal. A woman who has learned the proper methods of "self-examination" can find abnormalities of very small size, frequently 1.0 cm or less in diameter. If a woman reports finding a small lesion her discovery can never be disregarded.

Women report for routine physical examinations more frequently than in the past. The physician is obligated to examine the breasts of these patients carefully.

Examination of the breast, whether performed by the patient or the physician, should always include thorough, systematic palpation by the flat of the fingers with the breast tissue between the fingers and the chest wall while the patient is in a supine position. Breast tissue presenting the characteristics of a lump while the patient is upright may lose these attributes in the supine position. Small masses which are not possible to feel in the upright position may become easily palpable when the patient is supine.

The breast frequently harbors benign tumors, masses of small cysts, single cysts, adenosis, hyperplastic lobules or excessive fibrosis which may present themselves as lumps. Clinically these may be indistinguishable from carcinoma.

The firmness, difficulty of demarcation and fixation in the breast are important observations but are not conclusive. Physiologic changes induced



Figure 1.\*—Unsuspected lesion in right breast found by mammography in 87-year-old woman who had a left simple mastectomy for carcinoma in October, 1959. Invasive intraductal cancer found at operation.

by indigenous or administered hormones should be taken into account.

Almost any surgeon of experience has made errors in believing malignant tumors to be benign and vice versa. Regardless of experience and diagnostic acumen, one cannot rely upon clinical diagnosis. The hazard of error is too great.

Mammography, as performed by Egan and Gershon-Cohen, may assist in discovering important lesions earlier than can be done by physical examination.<sup>9,12,13</sup> This method requires special techniques and experience in interpretation. At the present time the Cancer Control Program of the U.S.P.H.S. is undertaking a study of the reproducibility of this method in other hands. As it becomes more widely used and experience with it becomes greater it may become a very useful tool.

Nipple discharge, except as a result of lactation, cannot be disregarded. Normally the duct orifices are plugged by desquamated epithelial cells. If there is sufficient accumulation of secretion within the ducts it will make its way out through the nipple.

If it is thick, yellow, greenish or greenish brown,



Figure 2.\*—Occult carcinoma left breast with axillary metastasis in a woman 66 years old. Lesion disclosed by mammography and confirmed at operation.

it usually has little significance. Discharge of this type usually is associated with dilated ducts or cystic disease. Fresh or old blood or serous discharge is of greater concern. Serous discharge may contain microscopic blood. Regardless of type, nipple discharge should be smeared and examined by the Papanicolaou technique.

The finding of blood in the smear is proof of intraductal disease. The appearance of the epithelial cells may be of value but usually does not demonstrate the nature of the underlying pathological process.

Blood may come from any portion of the breast. It is most common with intraductal papilloma. Intraductal papillomata occur most frequently in the larger ducts beneath or near the areola. It is usually possible to ascertain which duct or which segment of the breast produces the blood by careful palpation of the breast in concentric circles becoming smaller as they approach the nipple.

Diffuse papillomatosis of the duct system is not uncommon. There may be pronounced proliferation of cells, forming heaped up layers which may fill

\*Mammograms kindly supplied by G. M. Stevens, M.D., Palo Alto Clinic.

the ducts. Intraductal carcinoma with or without invasion may be seen.

When the area of origin of the blood cannot be demonstrated, the age of the patient becomes an important factor. Younger patients can be followed carefully, in the hope that the source of blood will become apparent. After the age of 50 likelihood that malignant disease is the cause progressively increases.<sup>7</sup>

In most instances no significant mass is present, but if a mass can be found the problem is simplified. Transillumination occasionally may reveal a duct filled with blood but usually is disappointing.

#### BIOPSY

Biopsy is mandatory when there is a dominant mass in the breast, or when a mass which differs from other masses is present or when a thickened area differing from the remaining tissue in either breast is found.

Needle biopsy has strong advocates and in experienced hands yields good results but is not as accurate as surgical biopsy. The principal advantages of this method are: 1. It may be done as an office procedure under local anesthesia. 2. It provides for the evacuation of cysts. 3. It diminishes the time of definitive operation if a positive diagnosis can be established in advance. The disadvantage is that it may not be productive of representative tissue and surgical biopsy will be required in addition. It is not devoid of elements of trauma. It is well suited to establish the diagnosis in inoperable cases.

Aspiration of cysts is a justifiable procedure if certain precautions be observed. Cyst fluid should be examined by the Papanicolaou method for evidence of malignant change. Bloody fluid is suggestive of malignant disease. The patient must be followed. If the mass does not disappear or recurs, surgical exploration is indicated.

Surgical biopsy should be performed under full anesthesia and usual operating room technique. Gentleness is requisite throughout. The breast should not be scrubbed. The skin should be gently cleaned with ether and the area painted with the tincture preparation of one of the usual agents.

Excisional biopsy is generally advocated but this author believes it should be limited to small lesions (1.5 cm or less). In larger lesions or those manifesting even minor degrees of skin attachment incisional biopsy, removing a small segment of representative tissue is less traumatic. Cancer is often cut across in excising larger lesions.

If the duct producing blood can be identified it can be probed and investigated surgically with the probe as a guide. Accurate diagnosis of intraductal lesions by frozen section may be impossible.

It may be difficult when good permanent sections are available.

Biopsy should be undertaken only when the facilities for frozen section preparations and a competent pathologist are available. It should not be performed unless the surgeon is prepared by training and experience and has adequate facilities to proceed at once with definitive therapy.

Occasionally the pathologist may suspect cancer but be unable to make a positive diagnosis by frozen section. The surgeon must rely upon the pathologist but should not expect the impossible of him. The majority of lesions where there is doubt ultimately prove to be benign. Under these circumstances the wound should be closed and a diagnosis based upon permanent sections awaited. A delay of 24 to 48 hours, while undesirable, has not been demonstrated to be harmful.<sup>14</sup> Performance of a destructive procedure without a positive diagnosis cannot be justified.

We do not employ "triple biopsy."

If a positive diagnosis of cancer be made, the wound of biopsy should be fulgurated until dry, packed with gauze and closed by two superimposed rows of continuous sutures to prevent seeding of cancer cells in the wound. The patient should be reprepared and redraped, and fresh gowns, gloves and instruments used in the definitive operation.

#### FACTORS INFLUENCING PROGNOSIS

Some factors influencing prognosis are subject to clinical evaluation. Others are not. It is necessary to speak in generalities because statistical information indicates only probabilities in the individual case.

Most observers agree that the more medial the lesion, the poorer the prognosis. Medial lesions have a greater tendency toward metastasis to the internal mammary nodes.

As a rule the larger the lesion, the poorer the prognosis but indolent tumors may achieve large size and remain confined to the breast. Size is not per se a determining factor. Wide metastasis may have occurred from small tumors before they were recognized.

In most instances, known duration and rate of growth depend upon observation by the patient. Where reliable information exists, the longer the tumor has been present and the more rapid its rate growth, the poorer the prognosis. Rapidly growing "inflammatory" carcinoma carries a bad prognosis.

Hormonal factors play a part. These are largely related to the age of the patient. Women less than 45 years of age have a better prognosis than older women if no metastasis has occurred. If metastasis has taken place it is poorer.<sup>34</sup> It must be assumed

that premenopausal, menopausal and early post-menopausal women have tumors which will be stimulated by estrogens.<sup>21</sup> Pregnancy, lactation and a late menopause adversely affect prognosis, but cancer in pregnant or lactating women does not have the hopeless prognosis formerly believed. If metastasis has occurred it is very poor.<sup>16</sup>

The histologic pattern is important. Intraductal carcinoma, extracellular mucinous cancer and medullary carcinoma with lymphocytic infiltration have a good prognosis. Invasive tumors of these types, once metastasis has taken place, behave much as other cancers of the breast.

The degree of cell differentiation plays an important part. The more closely the cells resemble normal cells, the better; and the more anaplastic they are, the poorer the prognosis. The degree of invasiveness is important.

An additional factor which we cannot evaluate is the frequent demonstration of cancer cells in the general circulation.<sup>10,29,6</sup> Present evidence indicates that there is a relationship of this phenomenon to the extent of disease. Cells have been demonstrated in the general circulation in the resting state and at the time of operation. The potential of these cells to establish distant metastasis is unknown.<sup>29,6</sup> Certainly some of them have this potential but under what circumstances remains to be established.

The majority of the factors mentioned are dependent upon little understood biologic processes. When we can understand these, we will be closer to a solution of the problem of cancer of the breast.

One fact stands out. The extent of the disease at the time of instituting treatment is the most important single factor in determining prognosis. The prognosis deteriorates if nodal metastasis has taken place. This is well exemplified by data in the Cancer Prognosis Manual<sup>20</sup> on almost 35,000 cases. When the disease is confined to the breast the five-year survival rate is 76 per cent. If axillary metastasis has taken place the figure falls to 35 per cent. If distant metastasis has occurred, the disease cannot be eliminated by any present means of therapy.

#### STAGING OF CANCER OF THE BREAST

*Clinical Staging.* Many classifications based on clinical observations exist. Some are relatively simple; some extremely complex. There has long been a need for a simple, yet adequately comprehensive classification which could have general acceptance. The Joint Committee on Cancer Staging and End Results Reporting has rendered a valuable service in producing one.\* It is based upon clinical findings relating to the tumor, lymph nodes and

clinical and roentgenographic determination of distant metastasis—tumor, lymph node and distant metastasis (T.N.M.).

The Committee consists of representatives of the American Cancer Society, the American College of Surgeons, the College of American Pathologists, the American College of Radiology, the American College of Physicians and the National Cancer Institute with statistical consultants from the National Institute of Health.

#### CRITERIA OF OPERABILITY

Many sets of criteria to determine operability in cancer of the breast have been compiled. Some are restrictive and some are liberal. The objective is to apply radical operation when it can be of benefit and to avoid it when it would be futile and perhaps harmful.

It is obvious that there is no hope of cure by operation when distant metastasis has occurred. The difficulty of demonstrating distant metastasis has already been mentioned. A complete bone survey may be desirable but is impractical in many instances. X-ray examination of the chest, lumbar spine, pelvis and upper femora suffices for practical purposes.

In the absence of evidence of distant metastasis, operability is determined by local examination. The findings indicating inoperability are: supraclavicular node metastasis; extensive skin involvement, especially of the inflammatory or satellite metastasis type; fixation of the tumor to the chest wall; large, matted or fixed axillary nodes; or some degree of combination of these findings.

If the local findings indicate inoperability the only justification for operation is to eliminate an ulcerating, discharging lesion or one in which ulceration is impending and there has been no response to other therapy. In these circumstances palliative removal is warranted.

#### CHOICE OF OPERATION

Operation offers the greatest hope of cure or long arrest of the disease. The important decision is to choose the operation which provides the best prognosis. All other considerations are secondary.

One must review the evidence as to the value of simple mastectomy compared with radical or extended radical mastectomy. It is obvious, at once, that if the disease were confined to the breast any of these procedures would eradicate it.

Simple mastectomy, as usually performed, is actually a partial mastectomy. The surface anatomical variations in the distribution of breast tissue are well known. In addition breast tissue may penetrate

\*To be reproduced in the completed "Cancer Studies" as Appendix #1. Copies obtainable from Committee on Cancer, 693 Sutter Street, San Francisco.

the pectoral fascia and be found in the underlying muscle. The tail of the breast may ascend high in the axilla. It is difficult to know when all breast tissue has been removed. Carcinoma has occurred in residual breast tissue after a supposed simple mastectomy for benign disease.

The most apparent limitation of simple mastectomy is that it does not remove the axillary nodes. These are the most common sites of metastasis.

Simple mastectomy followed by heavy irradiation as practiced by McWhirter is often cited as being equal to or producing better results than radical mastectomy. McWhirter has had a 42 per cent crude five-year survival rate.<sup>28</sup> Data of the California Tumor Registry for five-year observed survival 1942-1946 show 45.1 per cent for all stages and 67.3 per cent for localized disease. Corresponding rates for 1952-1956 are 51.2 per cent and 73.2 per cent respectively. Figures from the Connecticut Cancer Registry are similar. The difference is about 1 per cent. These figures are based almost entirely on radical mastectomy. The number of hospitals and the large number of surgeons included remove these statistics from the realm of "selected" series.

A reconfirmation study done on the 1942-1948 California cases established the accuracy of diagnosis as being at least 95.6 per cent. This study was carried out because the accuracy of diagnosis was questioned.<sup>25</sup>

The long time survival rates as computed from California Tumor Registry data are of great interest.<sup>26</sup> They are as follows:

	5 Years	10 Years	15 Years
All stages .....	49.7	32.0	22.5
Localized .....	72.1	51.4	38.1

The ten-year survival rate in McWhirter's series was 25 per cent for all stages.

When adjusted for normal life expectancy on the basis of the age distribution for females, the California figures show:

	5 Years	10 Years	15 Years
All stages .....	56.1	41.4	34.1
Localized .....	81.3	66.6	58.0

The Cancer Prognosis Manual<sup>20</sup> reports 17,926 cases treated by radical mastectomy alone with five and ten-year survival rates of 53.3 per cent and 35.3 per cent respectively. Many "selected" series show higher rates. The figures in the Manual for survival rates following simple mastectomy and irradiation are 44.9 per cent and 20.3 per cent at five and ten years.

Butcher, in a study of the material at the Barnes Hospital and Ellis Fischel Cancer Hospital, using the Tornberg classification and the probit method, reached the conclusion that about 75 per cent of

the patients would have been as well treated by simple mastectomy as by radical mastectomy but in the remaining 25 per cent the radical operation was superior.<sup>5</sup> This is a retrospective study based on information secured by operation. Unfortunately there are no criteria for applying it to operable cases in planning therapy.

One Danish series of alternate selections for extended radical operation of the Dahl-Iverson type and for simple mastectomy and irradiation showing substantially the same results by both methods has been reported.<sup>22,23</sup> There were about 250 cases in each group followed by three years. One hundred and eighty-two patients in each category were followed for five years. In such small series a few good or bad prognosis patients in either group could materially alter the results. There are other factors raising questions concerning the validity of drawing conclusions from this series.

It is difficult to compare different series from separate sources but one must conclude that the preponderance of evidence is on the side of the superiority of radical mastectomy in treatment of cancer of the breast. Aside from statistics is the fact that most surgeons of long experience have a number of patients free from demonstrable disease who had axillary metastasis—and in some cases extensive involvement—at the time of radical operation 15 to 25 years before. It is scarcely reasonable to assume that the same would have been true if simple mastectomy with or without irradiation had been employed.

If the operation is properly done, the difficulties following radical mastectomy are far less than investigators suggest. Some lymphedema occurs fairly frequently but it is rare for it to be severe. The degree of deformity is only slightly greater than that of simple mastectomy and no greater under clothing. The mortality rate at this time and under proper conditions is a small fraction of 1 per cent. The rate of complications is no greater than that of heavy irradiation and probably less.

The extension of radical mastectomy to include the internal mammary nodes in cases of central and medial lesions and those with axillary metastasis has been estimated by Urban to improve five-year survival by 10 per cent. There are a number of procedures designed to remove these nodes in continuity or separately. All add to the extent of the operation. For final evaluation these procedures must be more widely applied and over a longer period. This should be done in hospitals where adequate house staff is available and good follow-up can be carried out. This is a logical procedure based upon the known primary zones of spread of cancer of the breast. It is unlikely that the more extended procedures involving removal of the supraclavicular

lar or deep mediastinal nodes will improve results. If these nodes are involved it is reasonable to expect that there has been further spread of disease.

Simple mastectomy has limited value in the curative attack upon operable cancer of the breast. It is useful when a patient's general health or physiological age contraindicate a more extensive procedure. Chronological age alone is not a contraindication to radical mastectomy. Simple mastectomy or partial mastectomy is excellent for palliation when this is required.

#### **RADICAL MASTECTOMY**

After the wound of biopsy has been sealed and the patient reprepared and redraped, operation may proceed. It is wise to have two units of blood available.

The reader is referred to standard texts for the details of the operation. Volumes on surgery and particularly the more recent books on the breast present these in satisfactory fashion.

Many incisions have been designed for radical mastectomy. The placing and the nature of the incision are determined by the site of the lesion and the configuration of the patient. There is no reason to extend the incision to the arm where it leaves a visible and unsightly scar. Adequate exposure can be obtained by incisions which will be hidden by normal clothing.

The incision should be 7.5 cm or more from the lesion. It should be made without reference to subsequent closure. If the wound can be closed without tension, primary closure is desirable. Tension on the flaps jeopardizes the already doubtful blood supply to the margins. Plastic procedures to obtain closure further jeopardize it. If the wound cannot be closed easily the flaps should be sutured to the chest wall without tension and the residual defect covered by a split thickness skin graft taken from the thigh or abdomen.

Cases of implantation of tumor cells in the donor site have been reported. Fresh gloves, gowns and instruments should be used in taking the graft. If one is certain in advance that a graft will be necessary it can be taken before the operation and kept moist with sponges soaked in normal saline solution.

The flaps reflected should be so thin that practically no fat is left attached to them. In this way fewer of the superficial lymphatic channels are severed and there is less hazard of leaving cancer cells in the wound.

The skin should be fixed high in the axilla to obliterate dead space. A soft catheter with multiple openings placed in the axilla and attached to low pressure suction is helpful in removing blood and

lymph and encourages early adherence of the flaps to the chest wall.

Throughout the operation gentleness is essential. A maximum of sharp dissection and a minimum of manipulation of the breast and traumatic gauze dissection should be employed.

A properly performed radical mastectomy should leave the patient with full function of the corresponding upper extremity. Some lymphedema is fairly frequent but it is rarely of serious extent.

#### **ADJUVANT CHEMOTHERAPY**

The Surgical Adjuvant Breast Project has now issued Progress Report No. 15. The treated group was given thiotepa 0.8 mg per kilogram of body weight in divided doses (0.4 mg per kilogram on the day of operation and 0.2 mg per kilogram on each of the two succeeding days). The recurrence rate for the treated group with positive nodes was 29.5 per cent as compared with 39.5 per cent for the controls. The greatest advantage lies in premenopausal women with positive nodes. This is the only group in which the Committee advises the use of thiotepa. The results in this group are so favorable that it is doubtful that subsequent follow-up will change their purport.<sup>30</sup>

Other studies are in progress. When they are reported one will be able to judge what additional help we may obtain by systemic chemotherapy.

Local wound chemotherapy has been under investigation. It must be considered experimental at this time.<sup>6</sup>

#### **OOPHORECTOMY**

Oophorectomy in advanced and recurrent carcinoma of the breast has been established as a procedure of value in premenopausal, menopausal and early postmenopausal patients.<sup>37</sup> Its value in the treatment of patients with presumably curable carcinoma as a prophylactic procedure does not rest on as firm ground.

There are those who advocate it in all premenopausal women. Some surgeons apply it only when axillary metastasis has occurred, and some not at all. Some have extended it to include postmenopausal women to age 70 because of the incidence of cortical stromal hyperplasia.<sup>35</sup>

Several series indicate that ovarian suppression in premenopausal, menopausal and early postmenopausal women has prophylactic value.<sup>33,27</sup> It has been our custom to employ it in this group of patients.

It appears to be a logical procedure. Women in this age group must be presumed to have estrogen-influenced carcinoma.<sup>21</sup>



There is a conflict of opinion relative to the effectiveness of irradiation compared with surgical removal in suppressing ovarian function. It is stated by some investigators that the procedures are equally effective.<sup>24</sup> Others maintain that oophorectomy is superior.<sup>4,15</sup> Both conclusions are based in part on estrogen assay. With radiation there may be a delay of several months before estrogen suppression occurs. The effect of extirpation is almost immediate.

#### PALLIATIVE TREATMENT

The limited role of surgery of the breast in inoperable cases has been mentioned. Other procedures have broader application.

*Irradiation.* Major reliance is placed upon irradiation of the breast, axilla, internal mammary and supraclavicular areas in inoperable cancer of the breast. The primary tumor may shrink and ulcerated areas heal following irradiation. Local recurrence may disappear. The pain of bony metastasis usually is relieved and lytic areas may recalcify. There is wide variation in the degree and duration of favorable response. There are no reliable prognostic criteria. Sensitivity to irradiation can be determined only by therapeutic trial.

There are differences of opinion concerning the relative merits of orthovoltage and supervoltage therapy. It seems probable that one may be preferred under certain circumstances and the other in different circumstances.

Except for the treatment of individual lesions by irradiation in disseminated disease, additive or ablative, hormone therapy and chemotherapy provide better prospect of relief. Combinations of some or all these methods may well be employed simultaneously or in sequence. Sequential application is preferred in most instances.<sup>2</sup>

*Additive Hormone Therapy.* The use of estrogen in the treatment of women who are five years or more beyond the menopause and have metastatic or disseminated disease, provides reasonable prospect of relief. This therapy is most effective in soft part and pulmonary lesions. Treatment should be continued until progression of the disease can be demonstrated.

Androgens are more effective in postmenopausal than in younger women, but are used to advantage in the younger age group. In the case of skeletal lesions subjective relief may be obtained in the absence of evidence of objective improvement.

Adrenal corticoid therapy is useful in combatting the hypercalcemia of bony metastasis and may be more effective in treatment of some cases of visceral metastasis than estrogens and androgens. The claim of prolonged remissions when used early in disseminated disease requires confirmation.

The mechanism of action of the hormones is not understood. All have disadvantages. Those of estrogenic therapy are less than those of androgens and corticoids. Androgens have masculinizing properties although some of the more recent products have little or no masculinizing effect. The corticoids produce osteoporosis and other side effects. Progesterone preparations have been reported to produce significant remissions. These are devoid of estrogenic and androgenic properties.<sup>18</sup>

*Ablative Hormone Therapy.* Oophorectomy has been discussed. The prognosis in adrenalectomy resembles that of hypophysectomy in all respects. The mortality rates of about 5 per cent are identical. Objective improvement judged by rigid standards is subsequently equal, being about 30 per cent. Patients who respond favorably to either procedure live three times as long as those who do not—20 to 22 months compared with 6 to 7 months.

There is some evidence that the time interval between primary operation and recurrence is important with regard to the degree and duration of response to hormonal therapy. The longer the interval, the greater the likelihood of protracted response. The most favorable results may be obtained when the original operation was performed before the menopause and the recurrence became apparent after the menopause.

In general, no clear-cut prognostic criteria exist. The best indication of a probable response is a previous remission of three months or more following oophorectomy. There is some evidence that oophorectomy and hypophysectomy in sequence are more effective than if performed simultaneously.<sup>26,27</sup>

*Chemotherapy.* In addition to the use as surgical adjuvants, chemotherapeutic agents have value in the treatment of disseminated disease. Alkylating agents are as effective as radioactive isotopes in controlling pleural effusions caused by metastatic carcinoma. Some of the alkylating and antimetabolic compounds, especially the fluorinated pyrimidines and their derivatives, used systemically produce improvement in a substantial proportion of cases.<sup>18</sup>

These agents may be used alone or in conjunction with irradiation. It is reported that lower doses of both modalities are effective when the two are used simultaneously.<sup>15</sup>

All the chemical agents now employed are toxic. The bone marrow and the epithelium of the gastrointestinal tract are particularly susceptible to injury. Patients must be closely observed for evidence of toxicity and the drugs carefully administered by those who are familiar with their potentialities and hazards.<sup>18</sup>

*Summary.* Disseminated cancer of the breast is incurable but proper use of irradiation, additive and



ablative hormone therapy and chemical agents alone, in combinations or in sequence can induce objective and subjective improvement. They can prolong life to a limited extent and make it much more pleasant for those patients who respond. Occasionally the improvement is dramatic.

#### CONCLUSIONS

1. Any dominant lump, any mass differing from other masses and any localized thickening not found elsewhere in the breast must be considered to be cancer until proved otherwise.

2. Diagnosis must be established by biopsy and microscopic examination of representative tissue. Biopsy is a prerequisite to definitive therapy.

3. The most important factor in prognosis is the stage of the disease at the time of operation.

4. Surgical operation offers the patient with an operable lesion the best and perhaps the only chance of cure. The most widely applicable surgical procedure is the standard radical mastectomy and it offers the patient the best chance for cure or protracted arrest of the disease. Extension of the operation to include the internal mammary nodes is justified in certain cases. Simple mastectomy has very limited usefulness in curative efforts.

5. Prophylactic elimination of ovarian function is desirable in premenopausal, menopausal and early postmenopausal women. Oophorectomy has some advantages over ovarian suppression by irradiation.

6. Postoperative irradiation probably has value when axillary metastasis is present.

7. Irradiation is the best means of therapy for inoperable disease, local recurrence and bone metastasis.

8. Additive and ablative hormone therapy are of value when properly applied to patients with disseminated disease. Chemotherapy is useful but must be applied with extreme caution.

9. Every patient deserves kindly, understanding care and the benefit of palliative measures offering a reasonable prospect of relief.

10. There remain many unanswered questions in the problem of cancer of the breast. One must maintain an open mind and adjust his attitude toward therapy as research provides us with new information.

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#### REFERENCES

- Ackerman, L. V.: An evaluation of the treatment of cancer of the breast at the University of Edinburgh (Scotland) under the direction of Dr. Robert McWhirter, *Cancer*, 8:883, 1955.
- Artz, C. P., and Meena, A. L.: Interpretation of present-day information concerning treatment of cancer of the breast, *Surg. Clin. N.A.*, 42, 2:495, 1962.
- Berkson, J., Harrington, S. W., Clogett, O., Kirklin, J. W., Dockerty, M. D., and McDonald, J. R.: Mortality and survival in surgically treated cancer of the breast: A statistical summary of some experience at the Mayo Clinic, *Proc. Staff Meet., Mayo Clin.*, 32, 23:645, Nov. 1957.
- Block, G. E., Vial, A. B., and Pullen, F. W.: Estrogen excretion following operative and irradiation castration in cases of mammary cancer, *Surgery*, 43:415, 1958.
- Butcher, H. R., Jr.: Effectiveness of radical mastectomy for mammary cancer: An analysis of mortalities by the method of probits, *Ann. Surg.*, 159:383, Sept. 1961.
- Cole, W. H.: *Dissemination of Cancer, Prevention and Therapy*, Appleton-Century-Crofts, New York, 1961.
- Copeland, M. M., and Higgins, T. E.: Significance of discharge from the nipple in non-puerperal mammary conditions, *Ann. Surg.*, 151:635, May, 1960.
- Dao, T., and Moore, G. E.: Clinical observations of conditions which apparently enhance malignant cell survival, *S. G. & O.*, 112:191, Feb. 1961.
- Egan, R. L.: Experience with mammography in a tumor institution. Evaluation of 1,000 studies, *Radiology*, 75: 894, 1960.
- Engell, J. C.: Cancer cells in the circulating blood: Clinical study of occurrence of cancer cells in the peripheral blood and in venous blood draining tumor area at operation, *Acta Chir. Scand.*, 1955 Suppl., 201:1.
- Garland, L. H.: Changing concepts in the management of cancer of the breast, *New Physician*, 10, 11:433, 1961.
- Gershon-Cohen, J., Hermell, M. B., and Berger, S. M.: Detection of breast cancer by periodic X-ray examinations: A five-year survey, *J.A.M.A.*, 176:1114, July 1, 1961.
- Gershon-Cohen, J.: Roentgenography and management of breast cancer, *CA*, 12, 2:72, March-April 1962.
- Haagensen, C. D.: *Diseases of the Breast*, W. B. Saunders & Co., Philadelphia, 1956.
- Hall, B. E.: Personal Communication.
- Harrington, S. W.: Fifteen-year to forty-year survival rates following radical mastectomy for cancer of the breast, *Ann. Surg.*, 137:843, 1953.
- Horsley, J. S. III: Twenty years' experience with prophylactic bilateral oophorectomy in the treatment of cancer of the breast, *Ann. Surg.*, 155, 6:935, 1962.
- Huseby, R. A.: Hormone and chemotherapy in advanced breast cancer, *Proc. Fourth Nat. Cancer Conf.*, J. B. Lippincott Co., Philadelphia, 1960.
- Hutchinson, W. B., and Kiriluk, L. B.: Internal mammary node investigation in cancer of the breast, *Am. J. Surg.*, 92:151, Aug. 1956.
- James, A. G.: *Cancer Prognosis Manual*, American Cancer Society, New York City, 1959, p. 31.
- Jessiman, A. G., and Moore, F. D.: *Carcinoma of the Breast*, Little, Brown and Co., Boston, Mass., 1958.
- Kaae, S., and Johansen, Jr.: Breast cancer, *Acta Radiol. Suppl.*, 188, 1959.
- Kaae, S., and Johansen, H.: Breast cancer: Five-year results: Two random series of simple mastectomy with post-operative irradiation versus extended radical mastectomy, *Am. V. Roent.*, 87:1, 1962.
- Lewison, E. F.: Prophylactic versus therapeutic castration in the total treatment of breast cancer, *Proc. Fourth Nat. Cancer Conf.*, J. B. Lippincott Co., Philadelphia, 1960, p. 263.
- Linden, G., Cline, J. W., Wood, D. A., Guiss, L. W., and Breslow, L.: Validity of pathological diagnosis of breast cancer, *J.A.M.A.*, 173:143, May 14, 1960.
- Macdonald, I.: Indications of the fundamental biology of mammary carcinoma, *Proc. Third Nat. Cancer Conf.*, J. B. Lippincott Co., Philadelphia, 1957, p. 87.
- Macdonald, I.: Endocrine ablation in disseminated mammary carcinoma, *S. G. & O.*, 115:215, Oct. 1962.
- McWhirter, R.: Simple mastectomy and radiotherapy

in the treatment of breast cancer, *Brit. J. Radiol.*, 28:128, 1955.

29. Moore, G. E., Sandberg, A., and Schubarg, Jr.: Clinical and experimental observations of the occurrence and fate of tumour cells in the blood stream, *Ann. Surg.*, 146: 580, 1957.

30. Moore, G. E.: Personal Communication.

31. National Cancer Institute: End Results and Mortality Trends in Cancer, Monograph No. 6, Sept. 1961.

32. Paterson, R. J., and Russell, M. H.: Clinical trials in malignant disease III breast cancer: evaluation of post-operative radiotherapy, *J. Fac. Radiol. (Lond.)*, 10:175, 1959.

33. Paterson, R. J., and Russell, M. H.: Clinical trials in malignant disease II breast cancer: value of irradiation of the ovaries, *J. Fac. Radiol. (Lond.)*, 10:130, 1959.

34. Ryan, A. J., Griswold, M. H., Allen, E. P., Katzenstein, R., Greenberg, R., Keogh, J., and Wilder, C.: Breast cancer in Connecticut, 1935-1953. Study of 8,396 proved cases, *J.A.M.A.*, 167, 3:298, May 17, 1958.

35. Smith, G. V., and D. W.: Carcinoma of the breast: Results, evaluation of X-radiation and relation of age and surgical castration to length of survival, *S. G. & O.*, 97:508, 1953.

36. State of California Department of Public Health, unpublished data.

37. Taylor, S. G., III: Endocrine ablation in disseminated mammary carcinoma, *S. G. & O.*, 115:443, Oct. 1962.

38. Treves, N.: An evaluation of prophylactic castration in the treatment of mammary carcinoma, *Cancer*, 10:393, 1957.

